## REMARKS

In the Office Action dated January 16, 2003, the Examiner has made the restriction requirement final. Therefore, the elected Group II, Claims 8-27 and 39-68 are under current examination. Claims 1-7, 28-38 and 69-85 have been withdrawn from consideration. The application has been objected to as allegedly failing to comply with the requirements of 37 C.F.R §§ 1.821-1.825. The application has also been objected to for certain informalities. Claims 8-27, 39-49, 52, 64-68 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support. Claims 8-10, 14, 20 and 39 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly unclear. Claims 8-9, 12-14, 17-19, 22-27, 40, 42, 46, 49-50, 54 and 58 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 8-13, 15-27, 47-50, 52-54, 58 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Flax et al. (*Nat. Biotech* (1998) 16: 1033-1039) ("Flax et al."). Claims 39-49 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Thomson (U.S. Patent No. 5,843,780, published December 1, 1998) ("Thomson"). Claims 8-13, 15-27, 50-54 and 58 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Vescovi et al. (*Exp. Neurol* 156: 71-83, March 1999) ("Vescovi et al."). Claims 8, 10-13, 15, 16, 23-25, 50, 52-55, 58 and 59 have rejected under 35 U.S.C. 102(b) as allegedly anticipated by Anderson et al. (U.S. Patent No. 5,693,482, published December 2, 1997) ("Anderson et al."). Claims 8, 11-13, 15, 16, 23-25, 50-54 and 58 have been rejected under 35 U.S.C. 102(a) as allegedly anticipated by Johansson et al. (*Exp. Cell Res.* 253: 733-736, Dec. 1999) ("Johansson et al."). Claims 64-68 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Thomson when taken with Johansson et al. Claim 56 has been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Anderson et al. Claim 57 has been rejected under 35 U.S.C. 103(a) as

allegedly unpatentable over Anderson et al. when taken with van Inzen et al. (*Biochimica et Biophys Acta* 1312:21-26, 1996) ("van Inzen et al.").

Applicants, through the undersigned, wish to thank Examiners Thai-An N. Ton and Deborah Crouch for the courtesy and assistance provided in connection with a telephonic interview conducted on July 8, 2003.

During the course of interview, Applicants, through the undersigned, explained to the Examiners, among other things, that the neural progenitor cells (NPCs) derived *in vitro* from human ES cells in the present invention and the neural stem cells (NSCs) in the references cited by the Examiner are not the same but different products. The Examiners, while acknowledge that the NPCs and the NSCs have different behavior and require different culture conditions, states that different culture conditions are not sufficient to distinguish an NPC and an NSC. The Examiners require that Applicants should show that an NPC is **physically different** from an NSC, such as by having different markers.

During the course of the interview, Applicants also argued with respect to the enablement rejection of Claim 14. Applicants indicated that the references cited by the Examiner teach the experiments of stem cell/ES cell hybrids, while the present invention does not contemplate the NPC/ES cell hybrids. Therefore, the references cited by the Examiner are irrelevant. The Examiner agreed to consider Applicants' argument.

During the course of interview, Applicants also discussed certain proposed amendments to the claims with the Examiner. Agreement was not reached.

This response addresses each of the Examiner's objections and rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 1-7, 28-38 and 69-85 have been withdrawn from consideration. Applicants reserve the right to file one or more divisional applications drawn to the non-elected subject matter of Claims 1-7, 28-38 and 69-85.

The application has been objected to as allegedly failing to comply with requirements of 37 C.F.R 1.821-1.825. Specifically, the Examiner requires that each of the nucleotide sequences on page 63, lines 1-2 and 4, page 68, Table, and page 72, lines 2-5 must be accompanied by a SEQ ID NO.

In response, Applicants have amended the specification to recite the SEQ ID NOs. The specification, as amended, is in compliance with 37 C.F.R. §§ 1.821-1.825.

With respect to the Examiner's request that Applicants provide a substitute computer readable form (CRF) and a substitute paper copy of the Sequence Listing together with a Statement testifying that the content of the paper and computer readable copies are the same, Applicants respectfully submit that an initial CRF, paper copy of the Sequence Listing together with the Statement was filed with the U.S. Patent and Trademark Office on September 17, 2001. Applicants enclose herewith a courtesy copy of the same for the Examiner's convenience. Accordingly, the objection of the specification under 37 C.F.R. §§ 1.821-1.825 is obviated and withdrawal thereof is respectfully requested.

The application has been objected to under 37 C.F.R. § 1.84 or § 1.152, for certain drawing informalities. In response, Applicants have provided corrected drawings in compliance with 37 C.F.R. §§ 1.84 and 1.152. Therefore, the objection of the specification under 37 C.F.R. § 1.84 or § 1.152 is obviated and withdrawal thereof is respectfully requested.

The specification has been objected to for reciting "Clumpswere" on page 76, line 26. In response, Applicants submit that the recitation "Clumpswere" was an inadvertent

typographical error for "Clumps were." Applicants have amended the specification with the error corrected. Support for the amendment can be found throughout the specification, on page 76, line 29, for example. Accordingly, the objection for reciting "Clumpswere" is obviated.

Claims 8-27, 39-49, 52, 64-68 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support.

In the first instance, Applicants wish to clarify that an embodiment of the present invention is directed to embryonic stem (ES) cell-derived neural progenitor cells (NPCs). The NPCs and neural stem cells (NSCs) are distinct from each other and are different products. There are significant differences between these two types of cells with regard to, among other things, the stage of development that each originates from and their developmental potential.

Specifically, Applicants submit that human ES (hES) cell derived NPCs originate from the earliest stage of development of the neural system, which is the neuroectoderm. In contrast, NSCs originate from specific regions in the fetal and adult brains and are formed at yet an undetermined stage of brain development but at a later stage than the neuroectoderm stage of embryonic development. For example, the neural progenitors are derived from the very first stage of differentiation of hES cell colonies (after 2 weeks of differentiation inducing conditions). Moreover, the NPCs are derived from **early progenitors cells that are not expressing neural markers** but are destined to differentiate into neural progenitors in the appropriate culture conditions. These early progenitors are identified in distinct areas within the differentiating hES cell colonies. The early progenitors do not express markers of undifferentiated ES cells or the earliest neuroectodermal marker N-CAM (see Exhibit 1). The earliest neural cells within these colonies that express the neuroectodermal marker N-CAM can be demonstrated adjacent to and probably differentiating from these early progenitors. Indeed,

when clumps of these early progenitors are replated in serum-free medium, they form free floating neural spherical structures within 24 hours (Reubinoff, et al. (2001), Neural progenitors from human embryonic stem cells. *Nat. Biotechnol.* 19, 1134-40, enclosed as Exhibit 4).

Accordingly, the hES cell derived neural progenitors are derived from the very first stage of human neurogenesis.

During the course of the interview, the Examiner suggested that Applicants show NPCs are physically different from NSCs by having different markers. Applicants respectfully submit that marker is not a proper characteristic to distinguish two physically different cell types. In this regard, Applicants respectfully direct the Examiner's attention to a publication by Uchida et al. (Uchida, et al. (2000), Direct isolation of human central nervous system stem cells. *Proc. Natl. Acad. Sci. (U S A)* 97, 14720-14725, enclosed as Exhibit 6)("Uchida et al."), in which the authors derived human NSCs by sorting and selecting cells expressing the cell surface marker AC133 which is a marker of hematopoietic stem cells. The AC133 stem cells of Uchida et al., which have been isolated from human brains, are obviously not hematopoietic stem cells although they express the same AC133 marker as the hematopoietic stem cells. AC133 stem cells of Uchida et al. are characterized physically differently from hematopoietic stem cells mainly by their developmental potential, i.e., their capability to differentiate and give rise to neural cells.

Accordingly, even though hES cell-derived NPCs may share the expression of certain similar markers with the NSCs, this fact *per se* does not mean the NPCs are the same as the NSCs. In fact, it is known in the art that stem cells in general share the expression of some markers and genes. Recent expression profiles of ES and hematopoietic stem cells have demonstrated overlap in gene expression ("stemness"). Thus, it is not surprising these two cell

types share certain similar markers. More importantly, NPCs and NSCs have not been systematically compared yet. A marker that will differentiate between the two cell types may have not been found as yet.

Therefore, Applicants submit that the way to distinguish NSCs and NPCs at present is to consider parameters such as **developmental potential** and **gene expression profiles** and not their marker expression. The NPCs and NSCs differ with respect to their **developmental potential** and **gene expression profile**. These parameters may be measured and determined quite simply by on skilled in the art.

Applicants submit that, being the very first progenitors of the neural system, the NPCs have a broader developmental potential compared to the NSCs. The NPCs can be directed to differentiate *in vitro* into various types of neural cells, such as oligodendroglia cells, dopaminergic and serotoninergic neurons, by using the same signal molecules that direct the development into these cell types *in vivo* (Kim et al. (2002) Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature* 418, 50-56, enclosed as Exhibit 5; Brustle et al. (1999) Embryonic stem cell-derived glial precursors: a source of myelinating transplants. *Science* 285, 754-756, of record).

Moreover, Applicants submit that the inventors have demonstrated that human ES cell-derived neural progenitors also express the key regulatory genes along specific differentiation pathways *in vivo* such as differentiation into midbrain dopaminergic neurons (see Exhibit 2). While NSCs can give rise to the three major cell types of the CNS, their capability to express key genes along differentiation pathways *in vivo* or to respond to signal molecules that direct differentiation during normal development has not been demonstrated.

Applicants further submit that it has been demonstrated that the differentiation of human fetal derived NSCs into the three major cell types of the CNS is stable along propagation *in vitro*. The NSCs give rise to the same percentage of neurons following differentiation at various passage levels (Vescovi et al. (1999) Isolation and cloning of multipotential stem cells from the embryonic human CNS and establishment of transplantable human neural stem cell lines by epigenetic stimulation. *Exp. Neurol.* 156, 71-83, of record.). In contrast, the inventors have showed that the developmental potential of human ES cell derived neural progenitors is altered along their propagation *in vitro* (see Exhibit 3). Upon withdrawal of mitogens and plating on an appropriate substrate, early passage neural progenitors give rise mainly to neurons while late passage neural progenitors give rise to glia cells (see Exhibit 3). This developmental shift from neuronal to glial differentiation mimics a similar process that occurs during neural development *in vivo* where neurons are mainly formed at the early stage of development and glia cells at a later stage.

Further, Applicants submit that it has been demonstrated by the inventors and others in the art that the early neural progenitor cells can also be directed to differentiate into insulin producing cells. This result confirms the belief that NPCs do in fact have a more potent developmental potential. (Applicants can present this data upon request of the Examiner).

Given the evidence of different gene expression profiles and developmental potentials, Applicants submit that, while the NSCs and ES cell-derived neural progenitors and the NPCs may share the expression of certain markers and can both be propagated *in vitro* and give rise to the three neural cell lineages, the NPCs are more primitive precursors of the nervous system and have a broader developmental potential compared to NSCs. Therefore, ES cell-derived neural progenitors and the NSCs are different products.

In the Final Action, the Examiner acknowledges that the specification is enabling for undifferentiated pluripotent human ES cells. The Examiner alleges that the specification does not provide enabling support for undifferentiated totipotent human ES cells.

In response, Applicants have amended the claims to recite "undifferentiated pluripotent human ES cells."

The Examiner also specifically alleges that, although the specification broadly teaches that the cells of the present invention are capable of transdifferentiation, the specification does not provide specific teaching or guidance to show such transdifferentiation as claimed in Claim 14. The Examiner alleges that the state of art of transdifferentiation is unpredictable.

Applicants observe that, as the Examiner concedes, the specification teaches transdifferentiation of neural progenitors. For example, on page 45, last paragraph, the specification teaches that neural progenitors can transdifferentiate into mesodermal cells such as hemangioblast cells. Applicants note that the Examiner cites certain references, such as Kennea et al., and alleges that transdifferentiation is unpredictable and that the concept of stem cell transdifferentiation is not universally accepted. However, Applicants observe that the teachings of Kennea et al. are premised on co-culturing experiments involving NSCs or other adult stem cell and human ES cells. These experiments indicated that the resulting de-differentiated (transdifferentiated) cells were possibly NSC/ES cell hybrids. Thus, Kennea et al. conclude that transdifferentiation in all previous studies might be artifacts. For example, previous studies showed that bone marrow stem cells could transdifferentiate into cells of other types of tissue, e.g., blood cells or neurons. According to Kennea et al., a marrow stem cell/human ES cell hybrid might be formed during the experiments of these previous studies. Kennea et al. indicate that, because of the totipotent property of ES cells, the blood cells might actually be

differentiated from human ES cells, not transdifferentiated from marrow stem cells as currently recognized in the art.

In the first instance, Applicants respectfully submit that the present invention is directed to the NPCs, not the NSCs *per se*. Applicants further submit that NPCs of the present invention are not co-cultured with human ES cells. Furthermore, as earlier stated, the NPCs have been confirmed to possess much broader differentiation potential than the NSCs. Therefore, transdifferentiation of the NPCs, as recited in Claim 14, is predictable and one skilled in the art can make and use the claimed invention without undue experimentation. The references cited by the Examiner are irrelevant.

Accordingly, the rejection of Claims 8-27, 39-49, 52, 64-68 under 35 U.S.C. § 112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 8-10 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly unclear. Specifically, the Examiner alleges that the phrase "derived from" in Claim 8 is unclear. In response, Applicants have added the phrase "*in vitro*" to the end of Claim 8. Support for the amendment can be found throughout the specification, on page 18, lines 20-23, for example. Thus, Claim 8, as amended, is clear. Claims 9 and 10 are dependent on Claim 8. Accordingly, the rejection of Claims 8-10 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 8-9, 12-14, 17, 19, 22, 24-26, 40, 49 and 54 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner alleges that the phrase "capable of" implies a latent property. The Examiner requires that the conditions for a latent property must be clearly defined. The Examiner alleges that it is unclear as to whether the latent property is ever obtained.

Applicants respectfully submit that characteristics recited by the claims are capacities of cell proliferation, differentiation, grafting onto to recipient tissue and migrating after grafting. These capacities are either well known in the art or fully supported by the specification, on page 18, lines 16-28 and page 48, line 4 to page 49, line 9, for example. Thus, Applicants submit that the conditions for the capacities recited in Claims 8-9, 12-14, 17, 19, 22, 24-26, 40, 49 and 54 are clearly defined and that the phrase "capable of" is reasonably clear and definite under 35 U.S.C. § 112, second paragraph. Accordingly, the rejection of Claims 8-9, 12-14, 17, 19, 22, 24-26, 40, 49 and 54 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested

Claim 14 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly unclear. Specifically, the Examiner alleges that it is unclear what the recitation "other cell lineages" encompasses. In response, Applicants have amended Claim 14 by reciting "other progenitor cell lineages." Claim 14, as amended, is clear. Accordingly, the rejection of Claim 14 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 18-22 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner alleges that it is unclear what the term "extensively" in Claim 18 encompasses. The Examiner inquires as to what percentage or amount of a recipient [*sic*] brain would have to be incorporated into the recipient brain to constitute an extensive incorporation.

In the first instance, the Examiner's statement of the inquiry is unclear in itself. However, assuming that the Examiner may have meant to inquire into what constitutes extensive incorporation of neural progenitor cells into the recipient brain, Applicants respectfully direct the

Examiner's attention to the specification on page 23, lines 8-12, where description is provided regarding the meaning of "extensive incorporation" of neural progenitor cells. Thus, Claim 18, as written, is clear and precise and one skilled in the art can ascertain the metes and bounds of the invention. Claims 19-22 are dependent on Claim 18.

Accordingly, the rejection of Claims 18-22 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claim 20 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly unclear. Specifically the Examiner alleges that it is unclear what the term "responsive" in Claim 20 encompasses. The Examiner inquires as to how or in what way the cell responds to environmental signals. Applicants have amended Claim 20 to replace the recitation "is responsive" with the recitation "differentiates in response." Thus, Claim 20, as amended, is clear and definite. Accordingly, the rejection of Claim 20 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 23-27 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner alleges that there is insufficient antecedent basis for the recitation of "the enriched preparation." In response, Applicants have amended Claim 23 so that the preamble of the claim does not recite "enriched preparation of." Accordingly, the rejection of Claims 23-27 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 24, 42 and 46 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner alleges that it is unclear what the time frame of the term "prolonged" encompasses.

Applicants observe that the present application discloses generally "prolonged undifferentiated proliferation" on page 18, lines 25-29, page 22, lines 28-29, page 50, lines 25-27, and in Figure 7. The present application also provides a specific example, e.g., on page 78, lines 4-14, where the proliferation was maintained for up to 4 months, a prolonged period. The present application also discloses "maintaining a diploid karyotype during prolonged cultivation" generally on page 7, line 13 and page 19, lines 28-30; and "culturing the undifferentiated stem cells for prolonged periods" generally on page 7, lines 19-21, page 9, line 26 to page 10, line 2, page 35, lines 11-16, and page 39, lines 22-25. The specification also teaches a specific example of prolonged cultivation or culturing for prolonged periods, e.g., in Example 5 on page 74, lines 24-26.

In response, Applicants respectfully submit that the standard of definiteness is a reasonable degree of clarity and particularity. *MPEP* 2173.02. Definiteness must be analyzed, not in a vacuum, but in light of: (A) the content of the particular application disclosure; (B) the teaching of the prior art; and (C) the claim interpretation that would be given by one of the skilled in the art. *Id.* Therefore, given the teachings of the specification including the Examples, Applicants submit that an ordinary person skilled in the art is apprised of the time frames of the term "prolonged" in Claims 24, 42 and 46.

Applicants also note that the phrase "*in vivo*" in Claim 42 is an inadvertent typographical error. Applicants have made the correction in amended Claim 42. Support for the correction can be found in Claim 39.

Accordingly, the rejection of Claims 24, 42 and 46 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claim 27 has been rejected as allegedly indefinite for the recitation "may be". Applicants have amended Claim 27 to replace the phrase "may be" with "is." Accordingly, the rejection of Claim 27 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claim 39 has been rejected as allegedly unclear. Specifically, the Examiner alleges that it is unclear what the term "somatic differentiation" encompasses and how the cells are induced to differentiate "somatically." The Examiner alleges that the claim is further unclear for reciting the phrase "differentiating signal." The Examiner further alleges that it is not clear as to whether the term "and/or" is meant to further limit the claim.

Applicants submit that the phrase "somatic differentiation" is well defined in the art and is fully supported throughout the specification, e.g., on page 37, paragraphs 1-2. Applicants have also amended Claim 39, among other issues, to recite "a controlled differentiating condition." Support for the amendment can be found throughout the specification, on page 34, lines 18-21, for example. Claim 39, as amended, does not recite the phrases "differentiating signal" and "and/or."

Accordingly, the rejection of Claim 39 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claim 50 has been rejected as allegedly indefinite. The Examiner acknowledges that the ES cell-derived somatic cell progenitors would be induced to differentiate into somatic cells. However, the Examiner alleges that the recitation "inducing somatic cells" in the preamble of the claim is unclear. In response, Applicants have amended the preamble of Claim 50. Claim 50, as amended, is clear. Accordingly, the rejection of Claim 50 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claim 58 has been rejected as allegedly indefinite for the recitation "somatic cells induced." In response, Applicants have deleted the term "induced" from Claim 58. Thus, Claim 58, as amended, is clear and definite. Accordingly, the rejection of Claim 58 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 8-13, 15-27, 47-50, 52-54, 58 have been rejected under 35 U.S.C. 102(b), as allegedly anticipated by Flax et al. Specifically, the Examiner alleges that Claims 8, 11-13, 50 and 52 are product-by-process claims. Thus, the Examiner concludes that the product claimed by the present invention and the product taught by Flax et al. are identical.

Applicants observe that the claims of the present invention are directed to human neural progenitor cell lines derived from undifferentiated human ES cells (NPCs) *in vitro*. In contrast, Flax et al. teach stable clones of neural stem cells (NSCs) which were isolated from the human fetal telecephalon. *See* Flax et al. at 1033. As stated earlier, Applicants respectfully submit that NPCs and NSCs are physically different from each other with respect to, among other things, gene expression profiles and development potential. Thus, Applicants submit that Flax et al. teach a different product from that which is claimed in the present invention. Accordingly, the rejection of Claims 8-13, 15-27, 47-50, 52-54, 58 under 35 U.S.C. 102(b) as allegedly anticipated by Flax et al. is overcome and withdrawal thereof is respectfully requested.

Claims 39-49 have been rejected under 35 U.S.C. 102(b), as allegedly anticipated by Thomson. Specifically, the Examiner alleges that Claims 44 and 45 are product-by-process claims because the claims recite undifferentiated ES cells prepared by the method of either Claim 28 or 37, respectively. The Examiner also alleges that Claims 40 and 41 recite the expression of various undifferentiated embryonic stem cell markers which are inherent properties of undifferentiated ES cells.

Applicants observe that Thomson merely teaches the isolation of primate embryonic stem cells, such as from marmoset and rhesus monkey. Applicants observe that Thomson teaches that primate cells are kept in a non-differentiating state by the use of LIF and feeder cells (see culture conditions and methods of differentiation, at column 12, from line 40). Applicants also observe that Thomson teaches that the primate cells will "spontaneously differentiate" to an endodermal line when growing to achieve confluence. Thomson does not teach human ES cell derived neural progenitor cells. Thomson does not teach any specific example of isolation of human ES cells or a method of differentiating human ES cells into progenitor cells under controlled condition(s).

In an effort to expedite favorable prosecution, Applicants have further amended Claim 39 to recite "undifferentiated human pluripotent embryonic stem cells." Claim 39, as amended, is directed to methods of inducing somatic differentiation of undifferentiated human embryonic stem cells, *in vitro*, into progenitor cells under controlled differentiating conditions. Therefore, Applicants submit that Claim 39, as amended, is not anticipated by Thomson.

Thus, Thomson teaches a method quite different from that claimed in the present invention, such as Claim 39, as amended, which requires **controlled** differentiation. Thomson simply teaches uncontrolled differentiation (i.e., an "all-or-none" phenomenon) under situations where the supporting feeder layer is removed or when the cells, upon reaching confluence, are allowed to "over-grow."

Furthermore, Applicants observe that the controlled differentiation defined by Claim 39, as amended, is brought about by providing conditions which are **non-permissive** for stem cell renewal. By contrast, Thomson teaches differentiation under conditions that are **suitable for** stem cell renewal. For example, Thomson teaches that, when grown on embryonic

fibroblasts and allowed to grow for two weeks after achieving confluence, primate ES cells of the present invention will spontaneously differentiate (see column 12, from line 53). "Spontaneous differentiation" is commonly referred to by those skilled in the art as self renewal. Thus, even within an undifferentiated colony of hES cells grown on a suitable feeder layer, there is usually spontaneous differentiation of the hES cells along the outer boundary of the colony. Applicants submit that it is a common practice amongst the skilled artisans to cut out the central undifferentiated colonies prior to re-plating or passaging the cells. Applicants further submit that this passage means that there is still stem cell renewal taking place in the culture **during** the process of differentiation (i.e., stem cell renewal is not stopped before differentiation takes place, as is required by Claim 39).

With respect to Claims 44 and 45, Applicants submit that these claims are dependent on Claim 39 and therefore are not anticipated by Thomson.

Claims 44 and 45 are also dependent on Claims 28 and 37, respectively, which have been withdrawn from consideration. Applicants have amended Claims 44 and 45 to incorporate the subject matter of Claims 28 and 37, respectively. Support for the amendment can be found throughout the specification and in the original Claims 28, 37, and 44-45.

Accordingly, the rejection of Claims 39-49 under 35 U.S.C. 102(b) as allegedly anticipated by Thomson is overcome and withdrawal thereof is respectfully requested.

Claims 8-13, 15-27, 50-54 and 58 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Vescovi et al.

Vescovi et al. teach human neural embryonic stem cells which were isolated from post-conception human diencephalon. Applicants also observe that Vescovi et al. teach NSCs isolated from human embryo, while Claims 8-13, 15-27, 50-54 and 58 are directed to NPCs

derived from human ES cells *in vitro* and a method of controlled/reproducible differentiation of the NPCs.

Applicants respectfully submit that, prior to the present invention, one could grow NSCs using established methods such as taught by Vescovi. However, no one could successfully culture human ES cells as presently claimed. The present invention teaches human ES cells, human ES cell derived neural progenitor cells or NPCs (not NSCs) and a method of culturing and differentiating the human ES cells into progenitor under controlled conditions. Thus, Applicants submit that Vescovi et al. and the present invention teach different products made by different methods. Accordingly, the rejection of Claims 8-13, 15-27, 50-54 and 58 under 35 U.S.C. 102(b) as allegedly anticipated by Vescovi et al. is overcome and withdrawal thereof is respectfully requested.

Claims 8, 10-13, 15, 16, 23-25, 50, 52-55, 58 and 59 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Anderson et al.

Anderson et al. merely teach rat multipotent NSCs, including methods of isolation and differentiation of such cells. Claims 8, 10-13, 15, 16, 23-25, 50, 52-55, 58 and 59 are directed to human NPCs and methods for propagation and differentiation of such cells. Therefore, Anderson et al. do not anticipate the present invention. Accordingly, the rejection of Claims 8, 10-13, 15, 16, 23-25, 50, 52-55, 58 and 59 under 35 U.S.C. 102(b) as allegedly anticipated by Anderson et al. is overcome and withdrawal thereof is respectfully requested.

Claims 8, 11-13, 15, 16, 23-25, 50-54 and 58 have been rejected under 35 U.S.C. 102(a) as allegedly anticipated by Johansson et al.

Johansson et al. teach *bona fide* NSCs and the process of obtaining and culturing such cells. In contrast, the product and the process of making the product recited in Claims 8,

11-13, 15, 16, 23-25, 50-54 and 58 are directed to neural progenitor cells derived from undifferentiated human ES cells *in vitro* and the process of making thereof.

Applicants submit that NSCs are usually derived from neural tissue, either embryonic, fetal or adult, while ES cells are derived from an inner cell mass of a blastocyst and have the potential to differentiate into any cell lineage. As earlier stated, NSCs and NPCs are totally two different products.

With respect to Claim 50, the Examiner further rejects the claim for the recitation "embryonic stem cell derived." Applicants have amended the claim.

Thus, Claims 8, 11-13, 15, 16, 23-25, 50-54 and 58 are not anticipated by Johansson et al. Accordingly, the rejection of Claims 8, 11-13, 15, 16, 23-25, 50-54 and 58 under 35 U.S.C. 102(a) as allegedly anticipated by Johansson et al. is overcome and withdrawal thereof is respectfully requested.

Claims 64-68 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Thomson when taken with Johansson et al.

Applicants observe that Claims 64-68 are directed to methods of producing an enriched preparation of human ES cell derived neural progenitor cells. Applicants also observe that the undifferentiated human ES cells in the present invention are induced under controlled conditions to differentiate into neural progenitor cells.

Applicants note that Thomson merely teaches the isolation of primate ES cells, which will spontaneously differentiate when culturing in high density. Nowhere does Thomson teach or suggest that human ES cells are induced to differentiate into neural progenitor cells under controlled conditions, such as removing growth factors. Applicants also note, Johansson et al. merely teach *bona fide* neural stem cells and the process of obtaining and culturing such cells.

The rejection of claimed subject matter under 35 U.S.C. §103 requires that the suggestion to carry out the claimed invention must be found in the prior art, not in Applicants' disclosure. In re Vaeck, 947 F.2d 488, 492, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). Here, the suggestion to use the claimed methods to make an enriched preparation of human ES cells derived neural progenitor cells appears nowhere in the cited combination of Thomson and Johansson et al. Therefore, Applicants respectfully submit that the methods to make the enriched preparation of human ES cells derived neural progenitor cells, as instantly claimed, are not obvious in light of Thomson and Johansson et al.

In view of the foregoing remarks and the amendments, it is respectfully submitted that the present invention is non-obvious in view of Thomson and Johansson et al. Thus, applicants submit that the rejection of Claims 64-68 under 35 U.S.C. 103(a) is overcome. Withdrawal of the rejection is respectfully requested.

Claim 56 has been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Anderson et al.

Anderson et al. teach mammalian multipotent neural stem cells isolated from rats. As the Examiner acknowledges, Anderson et al. do not teach the culturing of neural stem cells on laminin.

Applicants submit that the rejection of claimed subject matter under 35 U.S.C. §103 requires that the suggestion to carry out the claimed invention must be found in the prior art, not in Applicants' disclosure. *Id.* Here, the suggestion to use laminin appears nowhere in Anderson et al. Furthermore, Applicants submit that culturing conditions for rodent neural stem cells and for human ES cells are not the same. Thus, a person skilled in the art would not have a reasonable expectation of success in applying the same conditions for rat neural stem cells to

human embryonic stem cells or neural progenitor cells derived therefrom. Therefore, Claim 56 is not obvious in light of Anderson et al. Accordingly, the rejection of Claim 56 under 35 U.S.C. 103(a) is overcome and withdrawal thereof is respectfully requested.

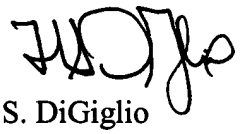
Claim 57 has been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Anderson et al. when taken with van Inzen et al.

Inzen et al. merely teach inducing rat ES cell differentiation with retinoic acid (RA). Applicants also observe that Anderson et al. teach mammalian multipotent neural stem cells isolated from rats.

In response, Applicants submit that a neural stem cell is different from an ES cell. Applicants further submit that getting a pluripotent ES cell to differentiate into a neural progenitor is totally unlike getting a multipotent neural stem cell to do the same – the conditions are different because the neural stem cells maybe clonal and there is no requirement for a feeder layer to grow neural stem cells. Further, as stated above, NPCs and NSCs are two totally different products. Thus, Applicants submit that a person skilled in the art would not reasonably expect to successfully use the method of Anderson et al. with the teaching of van Inzen et al. to achieve the process as recited in Claim 57. Accordingly, the rejection of Claim 57 under 35 U.S.C. 103(a) is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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